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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

THE BOARD OF APPEALS AND INTERFERENCES

Appellants	:	Thomas D. Madden et al.
Application No.	:	09/896,812
Filed	:	June 29, 2001
For	:	LIPOSOMAL ANTINEOPLASTIC DRUGS AND USES THEREOF
Examiner	:	Gollamudi S. Kishore
Art Unit	:	1615
Docket No.	:	480208.408
Date	:	June 19, 2006

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF FOR APPELLANT UNDER 37 C.F.R. § 1.192

Commissioner:

This brief is filed in support of Appellants' Appeal from the final rejection mailed October 3, 2005. Consideration of the application and reversal of the rejections are respectfully requested.

I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Inex Pharmaceuticals Corp.

II. RELATED APPEALS AND INTERFERENCES

Applicants are not aware of any related or pending Appeals, Interferences, or Judicial Proceedings.

III. STATUS OF CLAIMS

Claims 36, 43, and 66-68 are pending and are the subject of this appeal. Appellants request that claims 36, 43, 66, and 67 be considered as a first group that stand or fall together, but that claim 68 be considered as a second group that does not stand or fall with the claims of the first group on this issue.

Claims 33, 37, and 42 were cancelled pursuant to the Amendment filed October 9, 2003; claims 1-31 and 49-63 were cancelled pursuant to the Amendment filed January 21, 2005; and claims 32, 34, 35, 38-41, 44-48, 64, and 65 were cancelled pursuant to the Amendment filed July 11, 2005.

Claims 64-67 were added pursuant to the Amendment filed October 9, 2003, and claim 68 was added pursuant to the Amendment filed July 11, 2005.

IV. STATUS OF AMENDMENTS

All amendments have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Many antineoplastic agents have been encapsulated in liposomes, in order to reduce their toxicity and achieve superior pharmacokinetic properties. The pharmacokinetic properties of liposomal formulations of antineoplastic agents are largely determined by: (1) the rate at which the liposome is cleared from the blood; and (2) the rate at which the encapsulated antineoplastic agent is released from the liposome. For any particular liposomal formulation of an antineoplastic agent, each of these variables depends upon a variety of factors. For example, the rate at which an encapsulated antineoplastic agent is released from a liposome results from the combined effect of several factors, including: the particular lipids and other components of the liposome; the nature of the antineoplastic agent, *e.g.*, its size, solubility, and lipophilicity; and the amount of antineoplastic agent present in the liposome, *i.e.*, the drug:lipid ratio. The identification of specific liposomal formulations that possess superior pharmacokinetic properties for particular antineoplastic agents holds promise in the field of cancer treatment.

The present invention, in one embodiment, provides a liposomal vinorelbine formulation comprising a sphingomyelin and cholesterol-based liposome containing vinorelbine at a high drug:lipid ratio, wherein at least 50% of the vinorelbine in the liposome is precipitated, which results in the liposomal vinorelbine formulation having desirable drug retention properties (page 6, lines 12-23; Figures 1A and 2A). As set forth in independent claim 36, this liposomal vinorelbine formulation comprises:

- a liposome having vinorelbine in solution and precipitated vinorelbine, wherein
- the precipitated vinorelbine in said liposome is at least 50% of the total vinorelbine, wherein
- said liposome comprises sphingomyelin and cholesterol at a ratio in the range of about 75/25 mol%/mol% sphingomyelin/cholesterol to about 30/50 mol%/mol% sphingomyelin/cholesterol, and wherein
- the ratio of said vinorelbine to lipid is 0.1-0.5:1 (w/w).

This invention is based, in part, on the surprising discovery by Appellants that, at high drug:lipid ratios, vinorelbine precipitates within a liposome, leading to increased drug retention within the liposome (page 6, lines 24-31). This contravenes the conventional wisdom in the art, which was that higher drug:lipid ratios lead to increased drug leakage from liposomes. In addition, this invention is further based upon Appellants' identification of a specific combination of liposome components and high vinorelbine:lipid ratio range that provides superior liposomal retention of vinorelbine. Thus, the present invention meets a need for liposomal vinorelbine formulations having two advantageous properties previously thought to be incompatible: (1) high drug:lipid ratio; and (2) enhanced drug retention.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Are the pending claims unpatentable under 35 U.S.C. § 103 as obvious over the combination of U.S. Patent No. 6,110,491 ("Kirpotin") and U.S. Patent No. 5,543,152 ("Webb")?

Appellants submit that this question should be answered in the negative and that the rejection of the Examiner should be reversed.

VII. ARGUMENT

Claims 36, 43, and 66-68 stand rejected for being obvious over Kirpotin and Webb. Essentially, the Examiner has taken the position that Kirpotin describes advantages associated with having precipitated drug in a liposome, and Webb describes advantages associated with liposomes comprising sphingomyelin. The Examiner concludes that it would, therefore, be obvious for one of ordinary skill in the art to combine these two features to produce the claimed liposomal formulation, comprising a liposome having vinorelbine in solution and precipitated vinorelbine, wherein the precipitated vinorelbine in said liposome is at least 50% of the total vinorelbine, wherein said liposome comprises sphingomyelin and cholesterol at a ratio in the range of about 75/25 mol%/mol% sphingomyelin/cholesterol to about 30/50 mol%/mol% sphingomyelin/cholesterol, and wherein the ratio of said vinorelbine to lipid is 0.1-0.5:1 (w/w) (Office Action of March 9, 2005, page 5). Regarding the specifically recited drug:lipid and sphingomyelin:cholesterol ratios, the Examiner asserts that the drug:lipid ratios described in Kirpotin appear to fall within the claimed range (Office Action of March 9, 2005, page 5).

Applicants maintain their previously stated position that the Examiner has failed to establish a *prima facie* case of obviousness, since he has not established that the cited reference, alone or in combination, teach each element of the claimed invention, and he has not established that the skilled artisan would be motivated to modify the cited references to achieve the claimed invention (Amendment submitted July 11, 2005, pages 7 and 8, and Pre-Appeal Brief Request for Review submitted February 1, 2006, Remarks, pages 2-5).

A. LEGAL STANDARDS FOR OBVIOUSNESS REJECTIONS

To establish a *prima facie* case of obviousness, it must be established that the following three requirements are met: (1) the prior art must teach or suggest all of the claim limitations; (2) there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings; and (3) there must be a reasonable expectation of success. M.P.E.P., 8th Ed. § 2143.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and cannot be based on an applicant's disclosure. *In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991); *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). "[C]iting references which merely indicate the isolated elements are known is not a sufficient basis for concluding that the combination of elements would have been obvious." *Ex Parte Hiyamizu*, 10 USPQ 2d 1393, 1394 (POBAI 1988). In other words, the fact that teachings found in the prior art could be combined as proposed by an examiner does not make the combination obvious unless the examiner can point to some teaching or suggestion in the prior art supporting the combination. "[O]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *Carella v. Starlight Archery and Pro Line Co.*, 804 F.2d 135, 140 (Fed. Cir. 1986) (*citing ACS Hosp. Syss., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984). Similarly, "[t]he mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (*citing In re Gordo*n, 733 F.2d 900, 902 (Fed. Cir. 1984)). Although this statement is couched in terms of modifying the prior art, it is equally applicable to combining teachings found in the prior art.

Furthermore, a finding of obviousness must be based upon objective evidence demonstrating that the prior art taught or suggested the claimed combination. "[T]he factual inquiry whether to combine references must be thorough and searching." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52 (Fed. Cir. 2001). This factual question cannot "be resolved on subjective belief and unknown authority," *In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002); "it must be based on objective evidence of record." *Id.* at 1343. The correct standard for establishing obviousness is not merely a showing that it would have been "obvious to try" various unspecified combinations of elements. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Instead, the examiner must point to evidence demonstrating that the prior art taught or suggested the combination specifically claimed. In addition, the claimed invention must be considered "as a whole" when determining obviousness. 35 U.S.C. § 103(a).

B. CLAIMS 36, 43, 66, AND 67 ARE PATENTABLE OVER THE COMBINATION OF KIRPOTIN AND WEBB

The claims on appeal are patentable over the combination of Kirpotin and Webb, since these references do not teach each element of the claimed liposomal vinorelbine formulations. Furthermore, even assuming *arguendo* that Kirpotin and Webb taught each element individually or in some combinations, they do not provide any teaching or suggestion to combine all of the individual elements recited in the claims to achieve the specifically claimed liposomal vinorelbine formulations.

1. The Prior Art References Do Not Teach or Suggest All Claim Limitations

The Examiner has failed to establish that the prior art references describe each element of the claimed liposomal formulation. The pending claims are directed to a very specific liposomal vinorelbine formulation, wherein the liposome components, the drug, and the drug:lipid ratio are specified, based upon Appellants' discovery of a particular liposomal vinorelbine formulation having superior pharmacokinetic properties, including slower drug release. However, the Examiner has repeatedly failed to identify where either Kirpotin or Webb describe a liposomal vinorelbine formulation having a vinorelbine to lipid ratio of 0.1-0.5:1 (w/w). Appellants submit that neither of these references teach or suggest a liposomal vinorelbine formulation having this feature.

Webb fails to describe vinorelbine at all, and, when describing liposomal formulations comprising vincristine (another vinca alkaloid), Webb indicates that vincristine may be present at a drug:lipid ratio in the range of approximately 0.01-0.2:1 (w/w) (column 2, lines 37-38, and column 3, lines 10-11). This range is substantially different from the presently claimed range of 0.1-0.5:1 (w/w). Furthermore, it is clear that it is not mere oversight that leads Webb to describe such a low and narrow drug:lipid ratio for vincristine, since in a related continuation-in-part application, U.S. Patent No. 5,741,516, issued April 21, 1998, the drug:lipid ratio described for swainsonine is 0.01-0.5:1 (mol/mol), which is a much broader range. Thus, Webb clearly fails to teach liposomal vinorelbine at a ratio of 0.1-0.5:1 (w/w). Rather, the conclusion to be drawn from Webb appears to be that different drugs will have different preferred drug:lipid ratios. Thus, a description of a preferred drug:lipid ratio for one drug cannot render obvious a preferred drug:lipid ratio for a different drug.

Kirpotin, on the other hand, specifically recites vinorelbine in a long list of ionizable compounds that might be used in certain liposomal formulations described therein (column 6, line 18). However, regarding vinorelbine:lipid ratios, Kirpotin is completely silent. The only drug:lipid ratios described in Kirpotin are for the compound doxorubicin. For this drug, Kirpotin recites various doxorubicin:lipid ratios that result from loading liposomes containing different internal salts. There appears to be a wide range of resulting doxorubicin:lipid ratios, *e.g.,* from .008-.246:1 (mol/mol). Kirpotin does not provide a drug:lipid ratio for vinorelbine, and clearly does not describe the vinorelbine:lipid range of 0.1-0.5:1 (w/w) recited in the instant claims. The Examiner asserts that Kirpotin recites a drug:lipid ratio that falls within the claimed ratio. Even assuming *arguendo* that this is true, the recitation of one or more different doxorubicin:lipid ratios clearly does not amount to a description of a vinorelbine:lipid ratio of 0.1-0.5:1 (w/w), and, thus, cannot render the claimed liposomal formulation obvious.

As described in the instant specification and understood in the art, not all lipid formulations are equal for drug delivery purposes, and the optimal drug:lipid ratio varies for different drugs. Thus, extensive research continues in an effort to identify formulations that demonstrate preferred characteristics for drug loading and storage, drug administration, pharmacokinetics, biodistribution, leakage rates, tumor accumulation, toxicity, and other features (page 2, lines 21-29). Accordingly, the identification and selection of a preferred liposomal drug formulation with advantageous properties requires considerable effort and experimentation, and the resulting formulation is not obvious in light of a reference that fails to identify the specific features of a preferred liposomal formulation of a particular drug, *e.g.,* vinorelbine.

In addition, the skilled artisan would appreciate that the specific liposome components (*e.g.,* lipids), the particular drug, and the particular drug:lipid ratio are all variable features of liposomal formulations, each of which contributes to the pharmacokinetic properties of a liposomal drug formulation. Furthermore, these properties are not independent of each other, as the characteristics of a particular drug (*e.g.,* solubility, half-life, and size) will contribute to determining the best combination of these features. Thus, the identification of a specific combination of lipid components and drug:lipid ratio for a

particular drug, which provides superior pharmacokinetic properties for that drug, requires more than merely routine experimentation.

In light of the comments provided above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness of the pending claims over Kirpotin and Webb, since neither reference describes a liposomal vinorelbine formulation having the claimed drug:lipid ratio of 0.1-0.5:1 (w/w), which is a critical feature of the claimed liposomal vinorelbine formulations associated with their superior pharmacokinietic properties. This feature is not described in either reference, and would clearly not be considered common knowledge in the art. In his argument as to why this feature is obvious, the Examiner relies on Kirpotin, noting that Kirpotin teaches liposomes of various phospholipids and cholesterol and various drugs, with drug:lipid ratios that appear to fall within the claimed ratios (Office Action of October 3, 2005, page 2). However, since these liposomes do not comprise sphingomyelin and do not comprise vinorelbine at the claimed drug:lipid ratios, this reference absolutely fails to teach this feature. Accordingly, the Examiner has failed to provide the requisite evidence needed to demonstrate that the prior art taught of suggested each element of the claimed liposomal formulations.

2. The Prior Art Provides No Motivation to Combine the Teachings of the Prior Art References

The Examiner has clearly failed to establish that the skilled artisan would be motivated by the prior art references and knowledge in the art to achieve the specifically claimed liposomal vinorelbine formulation. The Examiner broadly asserts that the skilled artisan would be motivated to substitute sphingomyelin for phosphatidylcholine, since Webb teaches advantages of using sphingomyelin. However, the Examiner does not provide any statement indicating where motivation to use vinorelbine at the claimed drug:lipid ratio of 0.1-0.5:1 (w/w) is provided. Furthermore, the Examiner fails to provide any motivation as to why the skilled artisan would select this drug:lipid ratio when using sphingomyelin instead of phosphatidylcholine. It is well established that if obviousness is found by combining multiple references, there must also be some motivation to combine the prior art teachings in the particular manner claimed. *See, e.g., In re Kotzab*, 217 F.3d 1365 (Fed. Cir. 2000) "Particular findings must be made as to the reason the skilled artisan, with no knowledge of

the claimed invention, would have selected these components for combination in the manner claimed." 217 F.3d at 1371.

The cited prior art references and knowledge in the art fail to provide any motivation to combine various independent features of liposomal formulations to achieve the claimed liposomal vinorelbine formulations. As discussed above, the optimal drug:lipid ratio varies for different drugs. The specific liposome components (*e.g.*, lipids), the particular drug, and the particular drug:lipid ratio are all variable features of liposomal formulations, each of which contributes to the pharmacokinetic properties of a liposomal drug formulation. Furthermore, these properties are not independent of each other, as the characteristics of a particular drug (*e.g.*, solubility, half-life, and size) will contribute to determining the best combination of these features. Accordingly, the identification and selection of a preferred liposomal formulation for any particular drug requires considerable effort and experimentation and cannot be readily predicted by analogy to other drugs or formulations.

As previously submitted, neither Kirpotin nor Webb provide any motivation to combine all of the features recited in the pending claims, including: (1) the specified drug (vinorelbine); (2) the specified liposome (comprising 75/25-30/50 mol%/mol% sphingomyelin/cholesterol); and (3) the specified drug:lipid ratio (0.1-0.5:1 (w/w)), to achieve the specifically claimed liposomal vinorelbine formulations. Neither reference provides any teaching or suggestion to use vinorelbine at the claimed drug:lipid ratio, or any teaching or suggestion to produce liposomal formulations having the particular combination of claimed features.

More specifically, the Examiner has presented absolutely no motivational basis for the skilled artisan to use the specifically claimed combination of the drug vinorelbine in a sphingomyelin and cholesterol-based liposome, at a drug:lipid ratio of 0.1-0.5:1 (w/w). As noted above, Kirpotin describes a wide range of doxorubicin:lipid ratios, *e.g.*, from .008-.246:1 (mol/mol). Given the understanding that different drugs have preferred drug:lipid ratios, this description of a broad range of potential drug:lipid ratios for the drug doxorubicin can be considered, at best, a motivation to try various drug:lipid ratios within this broad range, which does not meet the legal requirements for establishing obviousness. Applicants can only conclude that the Examiner is applying impermissible hindsight, based

upon the teachings of the instant application, in drawing his conclusion that the presently claimed invention is obvious over Kirpotin and Webb.

C. CLAIM 68 IS PATENTABLE OVER THE COMBINATION OF KIRPOTIN AND WEBB

Claims 68 is patentable over the combination of Kirpotin and Webb, since these references do not teach each element of the claimed liposomal vinorelbine formulation and do not provide any teaching or suggestion to modify the teachings of the prior art to achieve the specifically claimed liposomal vinorelbine formulation. Claim 68 recites one specific embodiment of the claimed liposomal vinorelbine formulations, wherein the drug:lipid ratio is about 0.3:1 (w/w). Accordingly, the remarks provided above establishing the non-obviousness of claims 36, 43, 66, and 67 are equally applicable to claim 68.

Applicants further submit that while all of the claimed liposomal vinorelbine formulations provide unexpected advantageous pharmacokinetic properties, including enhanced drug retention, the liposomal vinorelbine formulation of claim 68 exhibits the greatest enhancement of drug retention, as shown in Figures 1A and 2A. The cited prior art references provide absolutely no teaching or motivation to achieve this vinorelbine:lipid ratio, with its superior pharmacokinetic properties and, therefore, cannot render this liposomal vinorelbine formulation obvious. Applicants submit that the Examiner has clearly failed to establish that the formulation of claim 68 is obvious over the cited references.

For the foregoing reasons, Applicants respectfully submit that the Examiner has not established that the claimed invention is obvious over the cited references. However, even assuming *arguendo* that the Examiner had made a *prima facie* case of obviousness, secondary considerations, including the surprising advantages associated with the claimed liposomal vinorelbine formulations, such as increased vinorelbine retention, demonstrate that the claimed invention is not obvious. Accordingly, Applicants respectfully request allowance of all pending claims.

Respectfully submitted,

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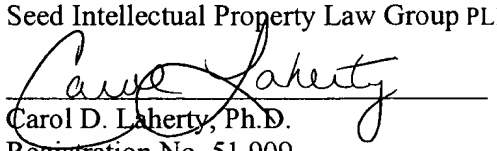

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VIII. CLAIMS APPENDIX

36. A liposomal formulation, said liposomal formulation comprising a liposome having vinorelbine in solution and precipitated vinorelbine, wherein the precipitated vinorelbine in said liposome is at least 50% of the total vinorelbine, wherein said liposome comprises sphingomyelin and cholesterol at a ratio in the range of about 75/25 mol%/mol% sphingomyelin/cholesterol to about 30/50 mol%/mol% sphingomyelin/cholesterol, and wherein the ratio of said vinorelbine to lipid is 0.1-0.5:1 (w/w).

43. The liposomal formulation of claim 36, wherein said liposome comprises sphingomyelin and cholesterol in a 55:45 molar ratio.

66. The liposomal formulation of claim 36, wherein the ratio of said vinorelbine to said lipid is about 0.1-0.3:1 (w/w).

67. The liposomal formulation of claim 36, wherein said liposome comprises sphingomyelin and cholesterol in a 50:50 molar ratio.

68. The liposomal formulation of claim 66, wherein the ratio of said vinorelbine to said lipid is about 0.3:1 (w/w).

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